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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,109	10/29/1999	Jacques Paris	GEI-073	6348

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EXAMINER	
QAZI, SABIHA NAIM	
ART UNIT	PAPER NUMBER
1628	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	09/423,109	PARIS ET AL.
	Examiner	Art Unit
	SABIHA QAZI	1628

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/11/11*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3,4,7,8 and 18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3,4,7,8 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☐ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

Non-Final Office Action

Claims 3, 4, 7, 8 and 18 are pending. Amendments are entered. No claim is allowed.

Summary of this Office Action

1. Continued Examination under 37 CFR 1.114
2. Information Disclosure Statement
3. Copending Applications
4. Specification
5. 35 USC § 112(2) Rejection
6. 35 USC § 103(a) Obviousness Rejection
7. Response to Remarks
8. Communication

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/13/11 has been entered.

Information Disclosure Statement

The IDS should be filed in this application if Applicants want any reference to be considered by the Examiner with reference to present application. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate

paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Copending Applications

Applicants must bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications, which are "material to patentability" of the application in question. MPEP 2001.06(b). See Dayco Products Inc. v. Total Containment Inc., 66 USPQ2d 1801 (CA FC 2003).

Specification

The priority of the application must be added in the beginning of the specification. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 103

Claims 3, 4, 7, 8 and 18 are rejected under 35 U.S.C. 103(a) as obvious over PLUNKETT et al. (US Re. 36,247), BLANC et al. (Clinical Therapeutics, 1998),

20(5), 901-912) and Casper (US 5,256,421). All the references teach the art, which embraces instantly, claimed invention. See the entire documents.

1. Determining the scope and contents of the prior art.

PLUNKETT teaches a method of hormonal treatment for menopausal disorders involving administration of progestagens and estrogens. The present invention provides a novel therapeutic method and composition involving the use of low dosage levels of estrogens and progestogens, which method is designed to avoid or minimize bleeding and prevent overstimulation of the lining of the uterus while producing favorable changes in blood lipids. In particular, the method involves continuous and uninterrupted administration of very small doses of a progestogen along with administration of an estrogen, the latter being cyclical. The reference provides a therapeutic method allowing for the administration of an estrogen, controlling hot flushes, restoring the vaginal mucosa to a healthier state, preventing the development of the dimineralization of bones as well as preventing changes in lipids which predispose to cardiovascular disease, over long periods of treatment, which method does not, however, initiate bleeding or increase the risk of endometrial carcinoma.

The reference further teaches a pharmaceutical composition for hormonal treatment of menopausal or post-menopausal disorders in a woman, which comprises a dosage unit of a progestogen and a dosage unit of an estrogen for continuous administration wherein the units comprise a **progestogen in the range of 0.025 to 30 mg and an estrogen in the range of 0.005 to 2.5 mg** together with a pharmaceutically acceptable inert carrier. The actual unit dosages are selected according to conventionally known methods, e.g. body weight of patient and biological activity of the hormones, with the ultimate goal of producing the desired result with **the minimum quantities of hormones**, (lines 62-68 in col. 3, lines 1-61 in column 4). See the entire document especially lines 40-51, col. 2; lines 63-67, col. 2; lines 1-67, col. 3; lines 18-25, and lines 1-5, col. 4; lines 46-50, col. 6.

The reference teaches continuous and uninterrupted administration of progestagen and estrogen. The actual unit dosage are selected according to conventionally known methods, e.g. body weight of patient and biological activity of hormones with the ultimate goal of producing the desired result with minimum quantities of hormones.

Plunkett does not disclose specifically nomegestrol acetate. The reference does not teach specifically nomegestrol acetate as presently claimed. It teaches progesterone which includes nomegestrol.

BLANC et al teaches continuous hormone replacement therapy combining nomegestrol acetate and gel, patch or oral estrogen in postmenopausal women This open-label, prospective, randomized, multicenter trial compared the incidence of amenorrhea in 54 postmenopausal women (mean age, 54.9 yr) who underwent six 4-wk cycles of continuous hormone replacement therapy combining a progestin- nomegestrol acetate 2.5 mg/d-plus one of three estrogens: percutaneous 17β-estradiol gel (1.5 mg/d, group A), transdermal 17β-estradiol patch (50 μg/d, group B), or oral estradiol valerate (2 mg/d, group C). Based on an intent-to-treat anal., the rate of amenorrhea varied significantly according to which estrogen preparation was used.

See the abstract of the invention; cols 1 and 2 on page 903 col. 2 on page 904, Table 1 on page 905, Figure on page 906; Table II on page 907. Prior art also teach that bleeding occurs when treatment is discontinued.

2. Ascertaining the differences between the prior art and the claims at issue.

PLUNKETT et al differs from the instant invention in that it does not specifically name nomegestrol acetate.

BLANC et al. teach the same combination, the ranges of the amounts higher for nomegestrol acetate than presently claimed. Prior art teaches 2.5 mg/dose whereas presently claimed amount is nomegestrol 0.625 to 1.25mg/dose

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

It would have been obvious to one skilled in the art to prepare additional beneficial compounds useful for hormone replace therapy in menopausal women using minimum quantities of hormones which does not initiate bleeding or increase the risk of endometrial carcinoma as has been taught by Plunkett to use lower amounts of hormones in combination of Blanc which teaches the combination of nomegestrol acetate (NOMAC) and estradiol valerate. It would have been obvious to one skilled in the art to select nomegestrol acetate from any progesterone because of the advantages of using it with lower doses.

Motivation is to use estrogen and progestagen continuously as taught by PLUNKETT et al. and use nomegestrol as progestagen because it gives in all patients' regular, progestagen-induced withdrawal of bleeding each month; and histological, ultra structural and biochemical changes were induced within the endometrium by all doses (0.5 mg, 1.0 mg; and 2.5 mg) is a potent progestogen. Blanc et al. teach same combination as combination of nomegestrol and estradiol. Thus, there has been ample motivation provided by the teachings of both the references cited above to prepare the instant invention in absence of any criticality or unexpected results. It would be obvious to one skilled in the art at the time of

invention to prepare a composition of NOMAC and estrogen to administer continuously combination of estrogen and nomegestrol as cited above. There is ample motivation provided by the prior art to select NOMAC because at high doses there is no bleeding pattern and have different effect on endometrium.

It is not unexpected in view of Plunkett in view of Blanc, one having ordinary skill in the art would give the minimal effective dose in order to avoid unwanted side effects. The doses of drugs also depends on the delivered formulation and dosage form, such as polymers used, coating of the dosage form, presence or absence of disintegrating agents or release enhancers. Etc.

Even if the doses are not overlapping, but close enough: "It has been held that where the claimed ranges overlap or lie inside ranges disclosed by the prior art, a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). It has been further held that a prima facie case of obviousness exists where the claimed ranges and the prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. *Titanium Meals Corp. of America v. Banner*, 778 F2d 775, 227 USPQ 773 (Fed. Cir. 1985)."

However, those of ordinary skill in the art would have been readily optimized effective dosages and concurrent administration regimens as determined by good medical practice and the clinical condition of the individual patient. Determination of the appropriate dosage for treatment involving each of the above mentioned formulations would have been routinely made by those of ordinary skill in the art and is within the ability of tasks routinely performed by them without undue experimentation, especially in light of the dosage information disclosed prior art and depending on variety of factors including the severity of the condition to be treated, the desired effect, possible of adverse reaction, and individual patient including age and body weight, etc.

The data does not commensurate with the scope of claims. The specification does not disclose how these ranges will be effective as has been claimed. Further, claim 18 contains estradiol esters, wherein the only ester mentioned is velerate.

In the light of the forgoing discussion, the Examiner's ultimate legal conclusion is that the subject matter defined by the instant claims would have been obvious within the meaning of 35 U.S.C. 103(a).

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 3, 4, 7, 8 and 18 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Following reasons apply:

3. It is unclear what is the meaning of "to effect the hormonal replacement therapy" in claim 18. Applicant is requested to explain.

Response to Remarks and Declaration

Applicant's response filed on 5/13/11 is hereby acknowledged. Since claims are amended rejections are withdrawn as cited above (beginning of the action). The obviousness rejection is re-written to address amended claim 18.

Applicants are arguing that Plunkett does not teach nomegestrol. The rejection was made in combination with Blanc reference which teaches nomegestrol. It has been decided by the court that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller,* 642 F,2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Further the test for obviousness is not whether the features of secondary reference may bodily incorporated into the structure of the primary reference, nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teaching of the references would have been suggested to those of ordinary skill in the art. See *In re Keller*, 642 F 2d 413, 208USPQ 871 9CCPA 1981).

Advantages of NOMAC was known at the time the invention filed.

It was known at the time the invention was filed that contrary to 19 nor testosterone derivatives, NOMAC does not contain any estrogenic and androgenic residual activity and also contrary to 17alpha-hydroxyprogesterone derivatives, it has a strong antigonadotropic activity. The citation of NOMAC in declaration brings original properties and comparison of table 1 (page 2) is not Applicants work. It was already known at the time when the invention was filed. The declaration should contain only the work done by the Applicants and proper

comparison. Applicant should not confuse their work with already known in the art without mentioning the source. Furthermore, in the declaration Applicant also cites WO 95/17194 and EP 025607 and Plummet's patent which is not relevant to the present claims.

Declaration further cites on page 4 that progestins continuously given with an estrogen induce an endometrial atrophy. Example 1 and 2 on page 6 of the declaration has been considered however, the art known at that time about advantages of NOMAC the combination of NOMAC and estradiol at the time the invention was filed would have been obvious. The present specification states that when the hormonal combination is given for a contraceptive purpose, the aim of the nomegestrol acetate is to stop ovulation and the aim of the estrogenic compound is to compensate for hypoestrogenia and ensure a better control of the cycle (Specification, page 7, lines 20-30). As such, the Specification discloses daily administering the composition from 21 to 25 days per month or 21 to 28 days, starting on the first day of the menstrual cycle (specification, page 7, lines 1-5, Page 11, lines 4-7).
Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

In paragraph after Table 3 on page 4 of the declaration that applicant has cited the advantages which are known in the art.

Communication

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sabiha Qazi whose telephone number is (571) 272-0622. The examiner can normally be reached on any business day except Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fetterolf Brandon can be reached on (571) 272-2919. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Sabiha Qazi/

Primary Examiner, Art Unit 1612